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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,063	12/06/2001	Kevin P. Baker	GNE.2830P1C3	8559

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EXAMINER	
HAMUD, FOZIA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,063	BAKER ET AL.	
	Examiner	Art Unit	
	Fozia M Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-36 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-36 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09/09/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt of Applicants' amendment and arguments, filed on 09 September 2004 is acknowledged. Claims 28-36 are currently amended and claim 37 is currently cancelled. Applicants' request to pursue any cancelled subject matter in subsequent continuation applications is noted.

Status of Claims:

1b. Claims 1-27 and 37 have been cancelled. Claims 28-36 and 38-40 are pending and under consideration.

1c. Receipt of Applicant's declarations under 37 C.F.R §1.132, filed by Dr. Avi Ashkenazi, Dr. Audrey Goddard and Dr. Paul Polakis filed on 096 September 2004 are also acknowledged.

2. ***Priority:***

Applicants submit that the results of the gene amplification assay disclosed in parent applications 60/162,506, filed 29 October 1999 priority for which has been claimed in the current application, provides a specific and substantial asserted utility for the claimed invention. Therefore, Applicants contend that the present application is entitled to the filing date of 29 October 1999.

This argument is not found persuasive. The claims of the instant invention are drawn to an isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO:77. However, said subject matter is not supported by the disclosure in the international application 60/162,506, filed 29 October 1999, since said the prior application does not provide a specific and substantial asserted utility or a well

established utility for the claimed invention. As was previously stated and will be discussed in the following sections, the gene amplification assay described in the parent application does not provide a specific and substantial asserted utility for the polypeptide of SEQ ID NO:77, because the assay shows that DNA sequences encoding the polypeptide of SEQ ID NO:77 is amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. However, the increased copy number of PRO1293 DNA in said tumors, does not provide a readily apparent use for the polypeptide of SEQ ID NO:77, because the assay does not show that the polypeptide is also amplified in these tumors.

Accordingly, the subject matter defined in claims 28-36 and 38-40 is afforded an effective filing date of 12/06/2001 which is the filing date of the current application.

Response to Applicants' arguments:

Claim Rejections under 35 U.S.C. §101/112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 28-36 and 38-40 stand rejected under 35 U.S.C. §101, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, and are also rejected under 35 U.S.C. 112, first paragraph, for

reasons of record set forth in the office actions mailed on 13 May 2004. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

3a. Applicant's arguments (submitted with the amendment of 09 September 2004) have been fully considered but are not found to be persuasive for the following reasons.

The Ashkenazi, Dr. Goddard and Polakis declarations under 37 CFR 1 .132 filed 09 September 2004 are also insufficient to overcome the rejection of claims 28-36 and 38-40 based upon 35 U.S.C. §101 and 112, first paragraph as set forth in the last Office action for the following reasons.

3b. Applicants argue that the gene amplification is an essential mechanism for oncogene activation, and that this assay is well described in Example 143 of the present application. Applicants submit that there was a 2 to 8 fold increase of PRO1293 gene in lung and colon tumors. Applicants review Dr. Goddards' declaration, which states that the gene amplification technique used in the present specification is sensitive enough to detect a 2 fold increase in gene copy number in a tumor tissue compared to a normal tissue is significant and useful in a diagnostic manner.

This argument is fully considered, but is not found persuasive. It is not disputed that the gene amplification assay is useful in diagnostic manner and that the assay is well described in the instant specification, however, the instant specification does not demonstrate that the increased copy number of PRO1293 DNA in lung and colon tumors, leads to an increased expression of PR01293 polypeptide in these tumors.

Therefore, since Applicants do not provide information regarding the level of expression, an activity, or a role in cancer or any other disease for the claimed PRO1293 polypeptide, the polypeptide lacks a substantial utility or well established utility.

Applicant argues that the WISP-2 or abl genes may be discrepancies. Applicant asserts that the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded polypeptide is likely to be expressed at an elevated level.

This has been fully considered but is not found to be persuasive. Regarding Pennica et al., the WISP-2 gene was still amplified as it was part of the amplification tested. Furthermore, Pennica et al. used a W1SP-2 specific probe to test for amplification. Although Pennica et al. raise a question regarding the mechanism of the amplification, it is not relevant to the issue at hand since the WISP gene was amplified without a corresponding increase in gene expression.

3c. Applicants review the evidentiary standard regarding the legal presumption of utility. Applicant argues that the USPTO has not met its burden of overcoming the presumption of the truth of an asserted utility. This has been fully considered but is not found to be persuasive.

The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of utility. Furthermore, the rejection does not question the presumption of truth, or credibility, of the asserted utility.

The asserted utilities of cancer diagnostics for the claimed antibody that binds to the polypeptide of SEQ ID NO:77, are credible and specific. However, they are not

substantial. The data set forth in the specification are preliminary at best. As the courts have discussed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct, 1966), an asserted utility must exist in currently available form. The specification indicates that the PRO1293 gene is amplified in certain cancers. However, the literature reports that gene amplification does not necessarily result in increased expression at the mRNA and polypeptide levels. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10- fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

3d. Applicant argues that even if a prima facie case of lack of utility has been established, it should be withdrawn on consideration of the totality of the evidence. Specifically, Applicant refers to the Ashkenazi declaration filed under 37 CFR § 1.132 with the amendment. The declaration and arguments assert that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment.

This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would also be useful; unfortunately, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not present in currently available form, and is not substantial. Applicant provides evidence in the form of a publication by Hanna et al., attached to the amendment. Applicant urges that the publication evidences that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

3e. Applicant refers to three additional articles (Orntoft et al., Hyman et al. and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fo1d gain of DNA

showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels.

This has been fully considered but is not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region, which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO1293 in the instant specification. That is, it is not clear whether or not PRO1293is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA over*expression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the polypeptides of the instant invention. Pollack et al. also used CGH technology, concentrating on large chromosome regions

showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the PRO1293 polypeptides have utility in the fields of cancer diagnostics are not substantial.

3f. Applicant presents a declaration by Dr. Polakis filed with the response under 37 CFR 1.132. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule.

This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding

increased mRNA levels of PRO1293 in lung or colon cancer samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 28-36 and 38-40 based upon 35 U.S.C. §101 and §112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. (See, Hu et al., cited in paragraph 3c of this office action).

3g. Applicant presents a declaration by Dr. Goddard filed with the response under 37 CFR §1.132, however, this declaration is insufficient to overcome the rejection of claims 28-36 and 38-40 based upon 35 U.S.C §101/112.

The Declaration submitted by Dr. Goddard has been fully considered, but is deemed unpersuasive to overcome the rejection of claims 28-36 and 38-40 based upon 35 U.S.C 101/112. Dr. Goddard submits references that describe the gene amplification technique used in the present application and references that attest to the use of this technique in diagnostic and prognostic fashion. Finally, Dr. Goddard states that the gene amplification technique used in the present specification is sensitive

enough to detect a 2 fold increase in gene copy number in a tumor tissue compared to a normal tissue is significant and useful in a diagnostic manner.

This argument is not found persuasive. Dr. Goddard's assertion that gene amplification is sensitive enough to detect a 2 fold increase and the a 2 fold increase in gene copy number in a tumor tissue compared to a normal tissue is significant and useful in a diagnostic manner, is correct. However, instant specification does not demonstrate that the increased copy number of PRO1293 DNA in lung and colon tumors, leads to an increased expression of PR01293 polypeptide in these tumors. Therefore, since Applicants do not provide information regarding the level of expression, an activity, or a role in cancer or any other disease for the PRO1293 polypeptide, the polypeptide lacks a substantial utility or well established utility.

Furthermore, should Applicants establish an activity for the polypeptide of SEQ ID NO: 77, instant specification would still fail to adequately enable an isolated polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95% or 99% to the polypeptide of SEQ ID NO:77. Due to the large quantity of experimentation necessary to determine all the polypeptides comprising an amino acid sequence that is at least 80%, 85%, 90%, 95% or 99% identical to the polypeptide of SEQ ID NO:77, and to screen an activity for them, the lack of direction/guidance presented in the specification regarding which variants of the polypeptide of SEQ ID NO:77 would retain the desired activity, the complex nature of the invention, the absence of working examples directed to variants of the polypeptide of SEQ ID NO:77, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity,

the unpredictability of the effects of mutation on the structure and function of the claimed polypeptide, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

For all of these reasons, the rejection claims 28-36 and 38-40 made under 35 U.S.C. §101 and §112 is maintained.

3h. Claims 28-32 also stand rejected under 35 U.S.C. 112, first paragraph.

Although the specification describes the structure of PRO1293 polypeptide, the skilled artisan would not be able to visualize the structure of the polypeptides having at least 80%, 85%, 90%, 95% or 99% identical to the polypeptide of SEQ ID NO:77, because the claims are not defined by structure and functional identity.

Applicant argues that the pending claims are drawn to a genus of polypeptides defined both by sequence and functional identity. This argument is not found persuasive, because although the claims recite both percent identity and functional language, the recited function is for the nucleic acid encoding the polypeptide of SEQ ID NO:77 and not for the polypeptide itself. The specification does not disclose a function for the polypeptide of SEQ ID NO:77, neither does the specification disclose a variant of the polypeptide of SEQ ID NO:77 that displays an activity.

Claim Rejections - 35 U.S.C. §102:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4a. Claims 28-36 and 38-40 stand rejected under U.S.C. § 102 (a) as being anticipated by Botstein et al (WO2000053751; published 14 September 2000).

Applicants submit that the current application is entitled to the filing date of 29 October 1999, (60/162,506). Hence, Applicants submit that WO2000053751 published on 14 September 2000 is not prior art under 102(a).

This argument is not found persuasive, because the invention of instant claims 28-32 are not entitled for the effective filing date of the priority application 29 October 1999, which is the filing date of 60/162,506, but is rather entitled to the filing date of the instant application, which is 12/06/2001, because the parent application does not teach how to use the claimed invention in a manner that satisfies the requirements, under 35 U.S.C. 112, first paragraph. See paragraph 3 of this office action.

Thus, WO2000053751 published on 14 September 2000 is prior art under 102(a).

Conclusion:

5. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M Hamud whose telephone number is (571) 272-0884. The examiner can normally be reached on Monday, Thursday-Friday, 6:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Fozia Hamud
Patent Examiner
Art Unit 1647
17 November 2004

JANET ANDRES
PRIMARY EXAMINER